Responses to executive demand in young adulthood differ by APOE genotype

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Responses to executive demand in young adulthood differ by *APOE* genotype

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Abstract

Despite evidence of a relationship between Apolipoprotein E (*APOE*) ε4+ and later-life cognitive decline, the lifespan effects of carrying an ε4+ allele on cognitive ageing are not well understood. Evidence of ε4+ advantages in early-life are inconsistent, but not inconsiderable. We explored the proposal that *APOE* ε4+ cognitive advantages arise only in response to complex and sensitive tasks targeting specific executive functions. We systematically manipulated executive demand within verbal fluency, decision-making, prospective memory, and sustained attention tasks. Participants aged 18-25 years (21 ε4+, 63 ε33) also completed a measure of subjective effort. Under low executive demand, ε4+ made fewer verbal fluency word repeats compared to ε33 carriers. Under high executive demand, ε4+ showed lower costs associated with performing concurrent tasks, greater switching errors, and more verbal fluency root repetition errors. Overall, ε4+ appeared to be showing working memory updating advantages under conditions of low executive demand, more effective resource allocation under elevated levels of executive demand, and errors indicating different strategy use compared to ε33 carriers, including speed-accuracy trade-offs.

Keywords

APOE ε4; cognitive aging; young adults; executive function; prospective memory; verbal fluency

Abbreviations: Analysis of variance (ANOVA); Apolipoprotein E (*APOE*); Early Cognitive and Leisure Activity (ECLA); Executive function (EF); high executive demand (HE); low executive demand (LE); Mean (*M*); Median (*Mdn*); MacArthur Scale of Subjective Social Status (MSSS); NASA task load index (NASA); National Adult Reading Test (NART); Prospective memory (PM); Rapid visual information processing (RVIP); Reaction time (RT); Standard deviation (SD)

1. Introduction

The relationship between carrying an *APOE* ε4 allele and poorer cognitive ageing, as well as the relationship between *APOE* ε4+ and elevated Alzheimer's disease risk, have been well established in later-life [1,2]. However, the effects of carrying an ε4 allele (ε4+) on cognitive function earlier in the lifespan are less well understood; indeed, it appears that the detrimental effects of ε4+ on cognitive functioning are not consistent across the life-span. In early-life, from infancy through to young adulthood, evidence has emerged of differences in cognitive performance between *APOE* genotypes. Young ε4+ have demonstrated advantages in cognitive performance across multiple cognitive domains [3–15]. Yet whilst support for young ε4+ cognitive advantages is not inconsiderable, evidence for cognitive differences driven by *APOE* genotype in youth is not entirely consistent [16–22]. Therefore, it is necessary to determine the conditions under which young ε4+ cognitive differences do arise to understand how the cumulative effects of carrying an ε4 allele emerge over the lifespan.

The impact of *APOE* on cognitive performance in early-life differs by cognitive process, which may underlie some of the inconsistent findings. Whilst there are some examples of young ε4+ carriers performing better than non-ε4 carriers (ε4-) on general neuropsychological batteries and IQ tests [8,10,15,23], most research demonstrating *APOE* genotype differences in youth used sensitive paradigms that place demands on specific cognitive processes rather than measuring general cognitive performance. This suggests that specific cognitive processes may be susceptible to *APOE* genotype effects in early-life. To date, ε4+ advantages in young adults have been seen in covert and sustained attention [5,9], as well as prospective, episodic, and spatial memory [5,6,11,12].

In support of this notion, genotype differences have been seen in simple processing speed and tasks related to executive functioning including executive switching [11,12,24], and in tests of verbal fluency [3–5,8,11]. Less sensitive attention, executive function, and associative learning tasks that resulted in performance levels approaching ceiling [25–27], and the use of composite measures of attention [28] failed to find any genotype differences, despite interrogating cognitive processes where genotype differences have previously been observed. This pattern of results has led to suggestions that frontally mediated processes may be differentially impacted by *APOE* genotype in youth [5], and that differential responses to conditions requiring increased executive engagement may underlie young ε4+ differences [11,26].

The most consistent *APOE* difference found in youth is an ε4+ verbal fluency advantage [3–5,8,11] even if the advantage was only subtle and related to processing speed, emerging throughout the verbal fluency task [5,29]. These results support the notion that increased frontally mediated task demands results in young ε4+ differences, as verbal fluency tasks include large executive control demands [30,31], and verbal fluency performance is dependent on frontal lobe processing [32].

Indeed, where a shorter version of the fluency task has been implemented, no *APOE* differences in verbal fluency have been observed [6] suggesting ε4+ may be more cognitively resilient to sustained executive processes, including working memory updating. Measures of general verbal ability have largely failed to report genotype differences [15,16,19,20,28,33–35], making it unlikely that *APOE* differences in general verbal ability underlie these verbal fluency findings, although there are exceptions [12,13]. Correspondingly, vocabulary size explains fluency performance less well than does updating ability, whereas the executive components of verbal fluency performance include response suppression, inhibitory control, effortful self-initiation, self-monitoring, cognitive flexibility, and processing speed [32,36–38].

Importantly, it may be executive requirements under conditions of sufficient cognitive demand that give rise to young ε4+ differences [5,39]. A sustained focused attention task that has consistently shown sensitivity to *APOE* genotype in youth [5,9] requires the continuous updating of working memory and allocation of attentional resources. Executive components of a prospective memory task showing a young ε4+ advantage in decision-making [5] include response inhibition, updating of working memory, and active monitoring [40–42].

Considering paradigm complexity, two studies have investigated genotype differences in response to task demand manipulations. Sinclair, Button, Munafò, Day, & Lewis [43] reported genotype differences on an n-back working memory task requiring updating in a very large sample of young adults. *APOE* ε4+ carriers appeared to show a speed-accuracy trade-off, although no consistent pattern of effects was discernible as n-back task demand increased. Considering only the most robust results, where confidence intervals did not cross zero, ε34 showed a reaction time advantage over ε33 carriers in both the 2-back and 3-back tasks. In an fMRI study, Foster, Kennedy, & Rodrigue [44] used a simple distance judgement task including visuospatial and working memory components and saw no behavioural differences by *APOE* genotype. In response to task difficulty, ε4+ showed a steeper decline in precuneus down modulation with age than ε4-, with down-modulation related to better cognitive performance. However, their sample spanned ages 20-86 years.

In a meta-analysis, Ihle et al. [39] considered whether executive function might underlie observed *APOE* differences in early-life cognitive function. Whilst they failed to find support for ε4+ advantages in youth or evidence of differential genotype responses to executive processes, the authors acknowledged that ε4+ cognitive advantages might arise only in complex and sensitive tasks targeting specific executive functions, highlighting the need for further research.

Therefore, the current study aimed to explicitly explore the young ε4+ response to task demand when systematically manipulating executive function. A growing literature suggests that the *APOE* genotypes may be differentially affected by early-life experiences including sociodemographic factors, cognitive resources, and leisure activity engagement [45,46]. Therefore, we ensured the homogeneity of relevant early-life factors within our study population. We predicted that ε4+ would outperform ε33 in conditions where elevated levels of executive engagement were required to perform well.

2. Method

2.1. Participants

One hundred and fifteen young adult participants (aged 18-25 years) were recruited through advertisements at local universities and from a database of previously *APOE* genotyped individuals. Inclusion criteria required participants to be fluent English speakers, non-dyslexic, have between 14-18 years education, and Caucasian. The initial screening phase included DNA collection and *APOE* genotyping of potential volunteers (for whom genotype information was not already held) by buccal swab, externally analysed by LGC Genomics to determine *APOE* genotypes (ε22, ε23, ε24, ε33, ε34, or ε44), derived from the *APOE* single nucleotide polymorphisms rs429358 and rd7412. Human Tissue Authority approved procedures were followed throughout, and both the initial screening phase and the cognitive testing phase were approved by the Life Sciences & Psychology Cluster-based Research Ethics Committee at the University of Sussex.

Participants provided written informed consent and were made aware that a double-blind triangulated procedure would be employed, therefore neither the participant nor the experimenter would know *APOE* genotype at any point during the study.

All participants completed the cognitive testing phase (conducted over a single session). Preliminary analysis of the cognitive performance data included all participants.

Subsequently, a subset of data from participants for whom we obtained APOE genotypes, comprising 21 ε4+ carriers and 63 ε33 carriers, was analysed to establish genotype-specific effects on cognitive performance. As the population norm, ε33 carriers were used as the control group, whilst ε34 and ε44 carriers formed an ε4 carrier group (ε4+); ε2 carriers were excluded. Participant Characteristics are shown in Table 1. Observed allelic frequencies were consistent with population norms [47].

Table 1
Descriptive statistics and baseline IQ, for the whole sample and APOE ε33 and ε4+ carriers separately

Measure	Whole sample (*N*=115)	ε33 (*n*=63)	ε4+ (*n*=21)	*p-value (genotype comparison)*
Sex[a]	21 male 94 female	9 male 54 female	8 male 13 female	.03*
Native language[a]	87 English 28 other	48 English 15 other	15 English 6 other	.77
Age[b]	20.50 (1.90)	20.52 (1.86)	20.43 (1.89)	.84
NART correct[b,c]	29.73 (4.94)	29.78 (5.22)	29.86 (4.81)	.95
MSSS[b]	06.07 (1.64)	06.06 (1.66)	06.55 (1.52)	.45
ECLA (early-life)[b]	99.57 (15.93)	99.98 (15.25)	99.90 (17.81)	.98
Parents education (years)[b]	26.88 (6.91)	27.27 (7.13)	29.35 (5.98)	.24

Notes: Mean (SD). National Adult Reading Test (NART). MacArthur Scale of Subjective Social Status (MSSS). Early Cognitive and Leisure Activity (ECLA). [a]Fisher's Exact Test, [b]Bootstrapped Independent t-test (2000 samples). ***p<.001, **p<.01, *p<.05. [c]Included in all analyses as a covariate – genotype results were unchanged after inclusion

2.2. Measures

2.2.1. Baseline IQ measure

The National Adult Reading Test (NART) was used to estimate verbal IQ through the pronunciation of 50 written words with irregular spellings [48].

2.2.2. Demographics and early-life factors

The MacArthur Scale of Subjective Social Status (MSSS) [49] was used to measure socioeconomic status (SES) on a 10-point scale (1= lowest, 10= highest).

Educational attainment of parental figures was measured on an 8-point scale (1 = lowest, 8 = highest). A summed score across up to two parental figures was calculated as an index of cognitive resources accessible in childhood [50].

A version of the Cognitive Reserve Index designed by Nucci, Mapelli, & Mondini [51] and modified for use with young adults was used to gather data on leisure activity engagement throughout early-life (see Appendix for full modified questionnaire). A

composite score extracted the frequency of Early Cognitive and Leisure Activity (ECLA) across childhood and adolescence.

2.3. Cognitive tests

For each cognitive task, low and high executive demand conditions were created. Low and high executive demand conditions were counterbalanced both within each test and across all three cognitive tasks. The NASA task load index (NASA; [52]) was used to gain a subjective measure of task demand after each condition, taken as a proxy of cognitive engagement required.

2.3.1. Verbal fluency

Participants verbally generated as many words as possible beginning with a given letter of the alphabet over 120s. Participants were instructed to avoid repeating words, proper nouns or root repetitions (e.g. run, running). Executive demand was manipulated in two ways. First, effortful self-initiation demands [31] were increased by including two levels of letter difficulty. In line with normative data on fluency difficulty by letter [53], and empirical studies confirming letter fluency differences [54,55], the letters F, A, and S (FAS) formed the low executive condition, and L, E, and V (LEV) the high executive condition. Second, working memory updating demands [56] were manipulated and compared over first vs second 60s of word generation.

2.3.2. Rapid visual information processing

The rapid visual information processing (RVIP) task [57] is a sustained attention task in which a continuous stream of digits (1-9) is presented sequentially in the centre of the computer monitor at a rate of 80 digits per minute (see Fig. 1). The participant monitors the digit stream for pre-specified 'target' sets, which occurred eight times within each 1-minute block across each 10-minute executive demand condition. Executive demand was manipulated in two ways. First, working memory updating and attentional switching demands were increased; participants had to respond to a target sequence of 3 odd digits (low executive demand – see Fig. 1A), or a target sequence of either 3 odd *or* 3 even numbers in a row (high executive demand – see Fig. 1B). Second, executive control and allocation of attentional resources were compared across the two five-minute blocks of each executive demand condition.

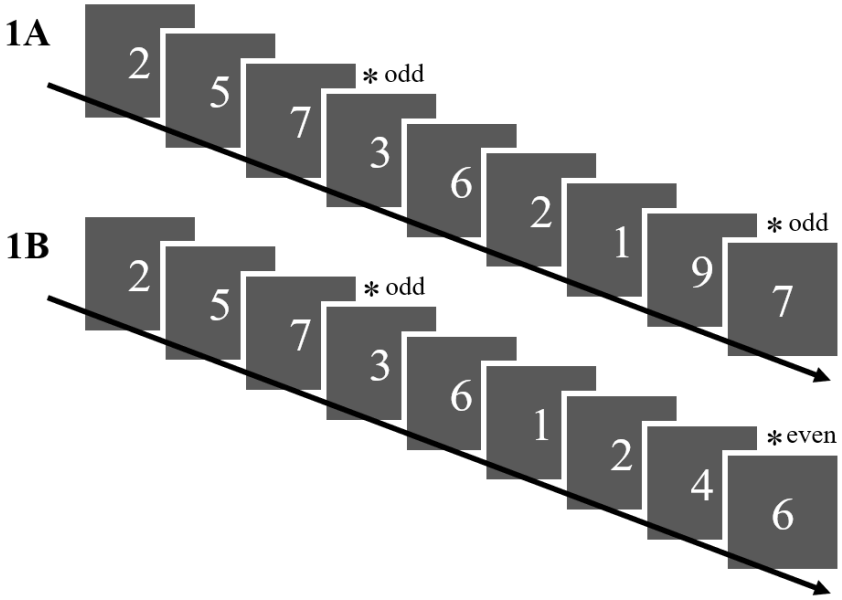

Fig. 1. Rapid visual information processing task. A continuous stream of digits was presented sequentially: target digits marked as *. 1A) Low executive demand: Participant responds to 3-odd numbers in a row. 1B) High executive demand: Participant responds to 3-odd or 3-even numbers in a row.

2.3.3. Prospective memory

A decision-making task with an additional prospective memory (PM) element was based on the Einstein et al. [58] PM paradigm. This task was divided into two task blocks; an ongoing task, and a prospective memory task. In the ongoing decision task, participants were required to make a word-related decision. A PM task was then added to the next block, with the additional instructions to press a target key whenever a certain syllable is presented, whilst also performing the ongoing decision-making task (constituting a non-focal PM task). A cognitively demanding 2-minute distractor task and a 1-minute questionnaire were presented between the PM instructions and the PM task block, with no reminder of the PM instructions given after the delay (see Fig. 2 for basic PM task procedure).

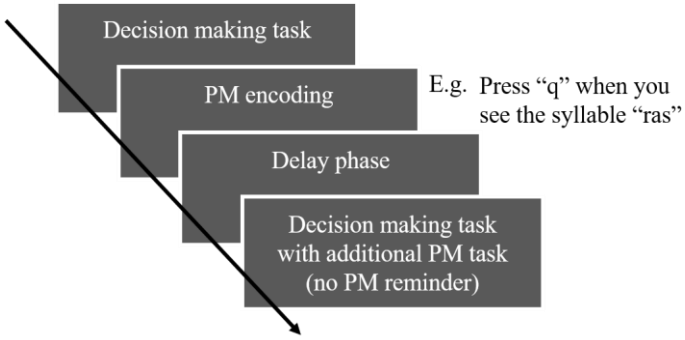

Fig. 2. Basic prospective memory task procedure.

The task was modified to manipulate executive demand by increasing the response suppression and executive control requirements of the ongoing task. Rather than the participant making one decision type throughout the ongoing task, they were required to switch between two different decision types – whether a word fit into a category, or whether a word contained ≤1 or 2≥ vowels, following Marsh, Hancock, and Hicks [59] and McNerney and West [60]. In the low executive condition, the participant completed one block of each decision type (decision switching by block - see Fig. 3A). In the high executive condition, the participant was instructed immediately prior (1000ms) to stimuli presentation whether to make a category or a vowel decision (decision switching by trial - see Fig. 3B).

All participants completed all four conditions: low executive demand, high executive demand, PM block and no-PM block. The ongoing task was always presented before the PM task, but all other conditions were counterbalanced across participants.

Within the low executive condition, the ongoing task comprised one block of 54 category decision trials (27 congruent, 27 incongruent – randomly presented), and one block of 54 vowel-decision trials (27 ≤1 vowel, 27 2≥ vowels– randomly presented), with the category or vowel blocks counterbalanced across participants. In the PM block, the ongoing task followed the same procedure, with the addition of three PM cues on trials 31, 72 and 102 (see Fig. 3C).

Within the high executive condition, the ongoing task comprised a block of 108 randomly presented category or vowel decision trials (27 congruent and 27 incongruent category decision trials, 27 ≤1 vowel and 27 2≥ vowel decision trials). In the PM block, the ongoing task followed the same procedure, with the addition of three PM cues on trials 31, 72 and 102 (with PM cues occurring on one category decision and two vowel decision trials) equalling 111 trials.

Word lists did not significantly differ in number of overall vowels (0-5), or word length. Match/no-match categories were randomly allocated across word lists, with no word list including fewer than 75% of the categories. No word list contained the same word cue twice, and no cue word was repeated more than twice across all word lists, and never for the same participant.

Participants completed practice trials before each executive demand condition, with feedback on accuracy and response speed. Stimulus presentation was the same regardless of executive demand condition or whether ongoing or PM task: decision trial/PM cue stimuli were presented for up to 7500ms, with the trial terminating upon response.

Upon completion of the entire task, participants were asked to recall the PM action and target (e.g. press Q when they saw the syllable "ras"). Participants then completed a target recognition task where they had to identify the two PM targets from a list with four additional distractor syllables. We did not exclude any participants who were able to recognise the PM targets, even if they failed to respond to any PM cue during the task; five participants who failed to respond to the PM targets during the task and failed to recognise the PM targets when cued were excluded.

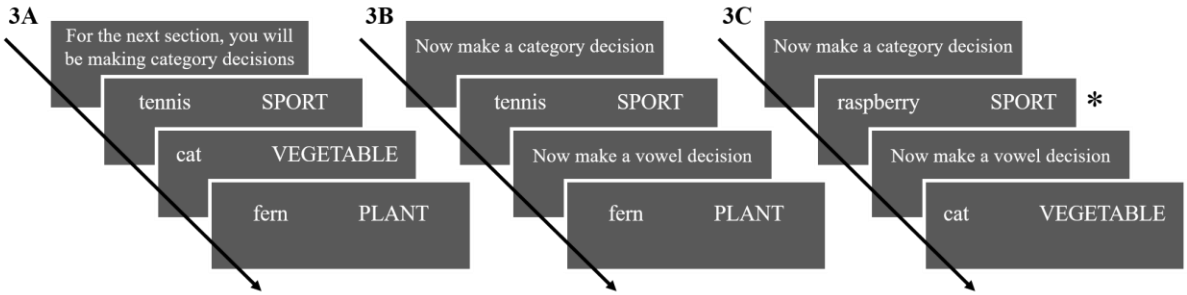

Fig. 3. Prospective memory task. 3A) low executive demand decision-making task: Participant responds to a block of 54 category decision trials then a block of 54 vowel decision trials (block order counterbalanced). 3B) high executive demand decision-making task: Participant responds to 108 randomly presented category or vowel decision trials. 3C) concurrent PM task: Participant additionally responds when they see a PM intention (e.g. syllable "ras") encoded earlier, in this example in the high executive demand block. PM target marked as *.

2.3.4. Digit symbol substitution

The digit symbol substitution test from the Wechsler Adult Intelligence Scale-Revised [61], was used as a filler task.

2.4. Statistical analysis

2.4.1. Verbal fluency analysis

The outcome variables were total correct words produced (across the three letters), and proportion of errors produced out of all words generated (including repeated words, root repetition, delayed root repetition, proper noun, foreign word, or non-word errors). Dichotomous measures (error/no error) were calculated for word repeat errors, root repetition errors, and delayed root repetition errors, due to low numbers of each individual error type.

Executive demand paradigm effectiveness was explored using 2 x 2 repeated measures ANOVAs, with letter manipulation (LEV, FAS) and duration manipulation (min 1, min 2) as the repeated measures factors, and correct words produced or proportion errors:correct words produced as the outcome variable.

Genotype differences were explored within the ε33/ε4+ genotype subgroup using 2 x 2 mixed ANOVAs, with either letter manipulation (LEV, FAS) or duration manipulation (min 1, min 2) as the repeated measures factor, and genotype (ε33, ε4+) as the independent-measures factor. NART-IQ was added as a covariate in these analyses. Genotype differences in dichotomous measures of word repeat, root repetition, and delayed root repetition errors (error/no error) were investigated using Fisher's Exact test.

2.4.2. Rapid visual information processing analysis

Reaction time (RT) for correctly identified targets, accuracy (percentage correctly identified targets), and false alarm rate (percentage false alarms) were the outcome variables. Additionally, a type I *d'* gave a measure of target detection whilst minimising the impact of response bias, with a higher *d'* showing better performance; this was calculated by subtracting the *z*-transformed proportion of false misses (FM) from the *z*-transformed proportion of correct hits (CH); $d' = z(CH) - z(FM)$. Trials where participants were +/-3 SDs from their own mean RT were excluded, and RT was recalculated. Two participants with a false alarm rate similar to their correct hit rate were excluded.

Paradigm effectiveness was explored using paired t-tests between low and high executive demand conditions, for RT, accuracy, false alarm rate, and type I *d'*. Performance over time was explored using a 2 x 10 repeated measures ANOVA, with executive demand (low, high) and time bin (minutes 1-10) as the repeated measures factors, and RT, accuracy or type I *d'* as the outcome variables.

Genotype differences in the same outcome variables were then examined within the ε33/ε4+ genotype subgroup, using 2 x 2 mixed ANOVAs, with executive demand (low, high) as the repeated-measures factor, and genotype (ε33, ε4+) as the independent-measures factor. Similarly, genotype differences over time were explored for each executive condition (low, high) separately using 2 x 10 mixed ANOVAs. NART-IQ was added as a covariate in these analyses.

2.4.3. Prospective memory analysis

Reaction time (RT) to correct decisions, and accuracy (percentage of correct decisions on valid trials) were the outcome variables for the ongoing decision-making task. Number of PM targets correctly identified, and the cost to RT and accuracy of holding the intention to respond to PM targets on ongoing decision-making task performance were the outcome variables for PM block; cost was calculated as both a continuous outcome (mean decrease in performance) and a dichotomous outcome (proportion of individuals showing a cost/no cost). In the high executive demand condition, number of switching errors was recorded; that is, making a vowel decision when prompted to make a category decision and vice versa. Outcomes were calculated across category and vowel decision trials, and for each decision type separately. Trials where participants were +/-3 SDs from their own mean RT were excluded, and RT was recalculated.

Paradigm effectiveness was explored using paired t-tests, comparing low and high executive demand conditions in RT and accuracy. Prospective memory cost was explored using a 2 x 2 repeated measures ANOVA, with PM block (ongoing /prospective memory block) and engagement block (low/high executive demand) as the repeated measures factors, and RT and accuracy as the outcome variables. Where there was a significant decrease in performance (slower RT or poorer accuracy) between the ongoing block and the PM block, a PM cost score was calculated. PM accuracy was explored in separate non-parametric analyses.

Genotype differences in decision-making (RT, accuracy) and PM cost to the ongoing task (RT, accuracy, switching errors) were then investigated in the ε33/ε4+ genotype subgroup. A 2 x 2 mixed ANOVA was conducted, using executive demand (low, high) as the repeated-measures factor, and genotype (ε33, ε4+) as the independent-measures factor. NART-IQ was added as a covariate in these analyses. Genotype differences in PM target identification accuracy were analysed using a Mann-Whitney Test, and differences in a dichotomous measure of cost (cost/no cost) for RT and accuracy were analysed using Fisher's Exact Test.

2.4.4. NASA task load index analysis

Paired t-tests and 2x2 repeated ANOVAs compared low and high demand conditions, as well as ongoing and decision-making block in the PM task. For the ε33/ε4+ genotype subgroup, separate Independent t-tests were conducted for each executive condition (low, high). The outcome measure was how effortful participants found the task.

2.4.4. Robust alternatives

Robust ANOVA alternatives were also conducted; mixed-ANOVAs using stringent 20% trimmed means and bootstrapped follow-up tests employing a modified one-step estimator based on Huber's Psi (2000 bootstrap samples per analysis) were implemented using the WRS2 R package [62], to ensure parameter estimates were not biased due to unequal sample sizes or leverage cases [63,64]. Robust analyses results were reported where they differed from non-robust analyses.

3. Results

3.1. Demographics

There were no significant genotype differences in any demographic, baseline IQ, or early-life factors ($p<.05$) except for sex, where the ε4+ group contained a higher proportion of males than the ε33 group ($p=.03$, Fisher's Exact Test; see Table 1).

3.2. Verbal fluency task

3.2.1. Correct word production

Across all participants, the number of correct words produced was higher in the low executive demand (LE: easy letters) condition (mean 30.13 words) than the high executive demand (HE: difficult letters) condition (mean 22.90 words), $F(1, 111) = 234.88$, $p<.001$, $\eta^2_p = .68$. Number of correct words produced was higher in the first minute (mean 34.43 words) than the second minute (mean 18.59 words), $F(1, 111) = 1318.07$, $p<.001$, $\eta^2_p = .99$. There was no interaction between letter and duration manipulations, ($F(1, 111) = 0.16$, $p=.69$, $\eta^2_p = .001$).

For the ε33/ε4+ subgroup, correct words produced are shown in Table 2. There were no genotype differences in correct word production by letter difficulty across the two-minute task duration, $F(1,81) = 0.03$, $p = .85$, $\eta^2_p = .00$, nor was there any genotype*difficulty interaction, $F(1,81) = 0.15$, $p = .70$, $\eta^2_p = .002$. When comparing the first vs second minute, there was no main effect of genotype in the LE condition, ($F(1, 81) = 0.08$, $p = .78$, $\eta^2_p = .001$), or HE condition, $F(1, 81) = 0.002$, $p = .97$, $\eta^2_p = .00$. There were no duration*genotype interactions in the LE or HE conditions (both $p > .05$). No genotype differences in correct words produced throughout the task by 15s time-bins were seen ($p > .05$).

Table 2
Verbal fluency performance, by APOE genotype

	Low executive demand		High executive demand	
	APOE ε33	APOE ε4+	APOE ε33	APOE ε4+
Correctly produced words	60.97 (15.16)	59.86 (18.00)	46.27 (12.74)	46.14 (10.66)
Errors (as % of total words generated):				
All error types	4.21 (3.82)	4.15 (4.05)	5.92 (5.09)	8.44 (7.87)
Word repeat errors*	0.76 (0.99)	0.33 (0.73)	0.68 (0.9)	0.62 (0.86)
Root repetition errors†	0.66 (2.50)	0.71 (1.42)	0.87 (1.93)	2.1 (3.19)
Delayed root repetition errors*	0.23 (0.56)	0.29 (0.56)	0.31 (0.69)	0.76 (1.18)
All other error types	1.21 (1.39)	1.48 (1.66)	1.16 (1.09)	1.57 (2.04)

Notes: Mean (SD). Genotype differences: *p <.05, †p <.07.

3.2.2. Errors produced

3.2.2.1. Proportion of errors. Across all participants, the proportion of errors produced was lower in the LE (easy letters) condition (mean 4.25% of all words generated) than the HE (difficult letters) condition (mean 6.74% of all words generated), $F(1,111) = 22.09$, $p<.001$, $\eta^2_p = .17$, and in the first minute (mean 4.71% of all words generated) than the second minute (mean 6.28% of all words generated), $F(1, 111) = 9.42$, $p = .003$, $\eta^2_p = .08$. There was no interaction between letter and duration manipulations, ($F(1, 111) = 1.52$, $p = .22$, $\eta^2_p = .01$).

When comparing letter difficulty (low, high) across the two-minute task duration within the ε33/ε4+ genotype subgroup, square-root transformed data were used due to unequal variances, shown in Table 2. No genotype differences in proportion of errors produced were seen, ($F(1, 81) = 0.42$, $p = .52$, $\eta^2_p = .01$), nor any difficulty*genotype interaction, ($F(1, 81) = 2.41$, $p = .12$, $\eta^2_p = .03$). When comparing the first vs second minute, there was no main effect of genotype in the LE condition, ($F(1, 81) = 0.01$, $p = .92$, $\eta^2_p = .00$), or HE condition, $F(1, 81) = 0.95$, $p = .33$, $\eta^2_p = .01$). There were no duration*genotype interactions in either executive demand condition (both $p > .05$).

3.2.2.2. Word repeats. There was a significant association between genotype and whether word repeat errors were made in the LE condition ($p = .04$, Fisher's Exact Test). Based on the odds ratio, the odds of ε33 carriers producing one or more word repeat errors was 3.73 times more likely than for ε4+ carriers.

3.2.2.3. Root repetitions. There was a marginally significant association between genotype and whether root repetition errors were made in minute 2 of the HE condition (p = .06, Fisher's Exact Test). Based on the odds ratio, the odds of ε4+ carriers producing one or more root repetition errors was 3.2 times higher than for ε33 carriers.

3.2.2.4. Delayed root repetitions. There was a significant association between genotype and whether delayed root repetition errors were made in the HE condition (p = .03, Fisher's Exact Test).). Based on the odds ratio, the odds of ε4+ carriers producing one or more root repetition errors was 3.43 times more than for ε33 carriers.

3.2.3. Subjective task difficulty

Across all participants, effort ratings in the HE condition (mean rating 69.91) were significantly higher than effort ratings in LE condition (mean rating 63.39), $t(112) = 5.20$, $p < .001$, $d = 0.51$.

Within the ε33/ε4+ subgroup, there was a marginally significant difference in effort ratings, as the LE (by letter) condition was rated as requiring less effort by ε4+ carriers than ε33 carriers, despite no genotype differences in correct word production performance, $t(81) = 1.96$, $p < .054$, $d = 0.46$. There was no genotype difference in effort ratings in the HE condition ($p > .05$).

3.3. Rapid Visual Information Processing task

3.3.1. Correct hits

3.3.1.1. Between executive demand conditions. Across all participants, hit accuracy was higher in the low executive demand (LE: odd sequences) condition (mean 89.27% correct) compared to the high executive demand (HE: odd or even sequences) condition (mean 59.94% correct), $t(110) = 23.44$, $p<.001$, $d = 2.48$.

There were no genotype differences in hit accuracy, $F(1,82) = 1.58$, $p = .21$, $\eta^2_p = .02$, nor any genotype*demand condition interaction, $F(1,82) = 0.80$, $p = .80$, $\eta^2_p = .001$, shown in Table 3.

Table 3
RVIP performance, by APOE genotype

APOE	Executive demand	Correct hits (%)	RT to correct hits (ms)
ε33	Low (odd sequences)	89.52 (10.18)	502.32 (60.15)
	High (odd/even sequences)	60.20 (17.81)	533.53 (72.05)
ε4+	Low (odd sequences)	85.54 (16.94)	507.37 (61.69)
	High (odd/even sequences)	55.36 (18.71)	550.38 (105.2)

Note: Mean (SD)

3.3.1.2. Over time. Across all participants, a 2x10 ANOVA demonstrated an interaction between demand condition*time, $F(9,855) = 7.76$, $p < .001$, $\eta^2_p = .08$. Secondary analyses confirmed that the percentage hit accuracy significantly differed over time in the LE condition, $F(7.82,852.80) = 2.02$, $p = .04$, $\eta^2_p = .02$, driven by decreases in accuracy from the 2nd to the 4th minute ($p = .02$). A similar difference in hit accuracy over time was seen in the HE condition, $F(9,864) = 10.67$, $p < .001$, $\eta^2_p = .10$, this time driven by accuracy in the first minute being higher than all other minutes ($p<.01$), and accuracy in the 5th minute being lower than the 6th minute ($p = .01$).

There were no genotype differences in hit accuracy over time in the LE condition, $F(1,82) = 1.69$, $p = .20$, $\eta^2_p = .02$, or HE condition, $F(1,82) = 1.14$, $p = .29$, $\eta^2_p = .01$, nor any genotype*time interactions in the LE condition, $F(7.73,634.09) = 0.59$, $p = .78$, $\eta^2_p = .01$, or HE condition, $F(9,738) = 0.32$, $p = .97$, $\eta^2_p = .004$.

3.3.2. Reaction time

3.3.2.1. Between demand conditions. Across all participants, reaction time to correctly identified targets was faster in the LE (mean 506.27 ms) compared to the HE condition (mean 540.40 ms), $t(110) = -6.38$, $p< .001$, $d = 0.64$.

There were no genotype differences in reaction times to correct hits, $F(1,82) = 0.43$, $p = .51$, $\eta^2_p = .01$, nor any genotype*demand condition interaction on reaction times, $F(1,82) = 0.71$, $p = .40$, $\eta^2_p = .01$, shown in Table 3.

3.3.2.2. Over time. Across all participants, a 2x10 ANOVA demonstrated a main effect of demand condition, $F(1,95) = 33.50$, $p < .001$, $\eta^2_p = .26$, a main effect of time, $F(7.91,751.15) = 2.08$, $p = .04$, $\eta^2_p = .02$, but no demand condition*time interaction, $F(7.37,700.36) = 1.71$, $p = .10$, $\eta^2_p = .02$.

There were no genotype differences in reaction times to correct hits over time in the LE condition, $F(1,82) = 0.002$, $p = .96$, $\eta^2_p = .00$, or HE condition, $F(1,82) = 1.57$, $p = .22$, $\eta^2_p = .02$, nor any genotype*time interactions in the low demand condition, $F(5.36,433.88) = 0.66$, $p = .67$, $\eta^2_p = .01$, or high demand condition, $F(7.03,499.62) = 1.60$, $p = .13$, $\eta^2_p = .02$.

3.3.3. False hits

3.3.3.1. Between demand conditions. Across all participants, the percentage of false hits was lower in the LE (mean 0.52%) compared to the HE condition (mean 0.81%), $t(110) = -3.30$, $p = .001$, $d = 0.41$.

There were no genotype differences in percentage of false hits, $F(1,82) = 0.27$, $p = .61$, $\eta^2_p = .01$, nor any genotype*demand condition interaction on percentage of false hits, $F(1,82) = 1.12$, $p = .29$, $\eta^2_p = .02$ (see Table 3). However, a robust mixed ANOVA using 20% trimmed means demonstrated an interaction ($p < .001$); bootstrapped simple main effects demonstrated genotype differences lay in the low demand condition, with ε4+ making fewer false hits (0.17%) compared to ε4+ carriers (0.31%), $Y_t = 0.10$, $p = .04$, 95% CI [0.01, 0.33], robust $\hat{\xi} = 0.31$. There was a significant increase in false hits from low to high demand for both for ε4+ (mean increase 0.42), $T_y = 5.10$, $p < .001$, 95% CI [0.56, 0.24], robust $\hat{\xi} = 0.71$, and for ε33 (mean increase 0.16), $T_y = 2.88$, $p < .001$, 95% CI [0.27, 0.05], robust $\hat{\xi} = 0.33$ (see Fig. 4), although ε4+ carriers showed a much larger effect size.

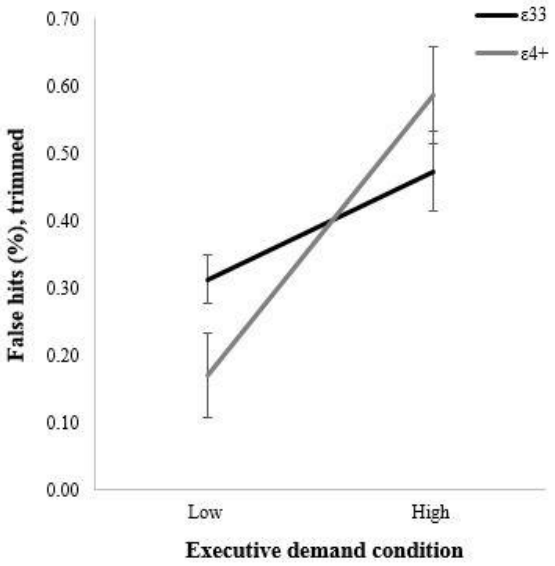

Fig. 4. False hits (with trimmed means) between executive demand conditions, by *APOE* genotype (+/- 1SEM)

3.3.3.2. Over time. The low number of false hits preclude analysis by time.

3.3.4. Type 1 d' (signal detection)

3.3.4.1. Between demand conditions. Across all participants, *d'* scores were higher in the low demand (mean 4.15) compared to the high demand condition (mean 2.84), $t(110) = 21.99$, $p < .001$, $d = 2.11$.

There were no genotype differences in *d'* scores, $F(1,82) = 0.21$, $p = .65$, $\eta^2_p = .003$, but there was a genotype*time interaction, $F(1,82) = 5.87$, $p = .02$, $\eta^2_p = .07$. Simple main effects demonstrated no genotype differences in *d'* in the low demand condition, $t(25.80) = -0.45$, $p = .65$, $d = 0.13$, or high demand condition, $t(82) = 1.58$, $p = .12$, $d = .41$. There was a significant decline in *d'* from low demand to high demand for ε33, $F(1,62) = 293.93$, $p < .001$, $\eta^2_p = .83$, and for ε4+, $F(1,20) = 113.65$, $p < .001$, $\eta^2_p = .85$ (see Fig. 5). However, these results (seen in Table 3) must be interpreted with caution, due to inequality of error variances, and indeed, a robust mixed ANOVA using modified one-step estimation demonstrated a lower significance value for the genotype*time interaction of $p = .086$.

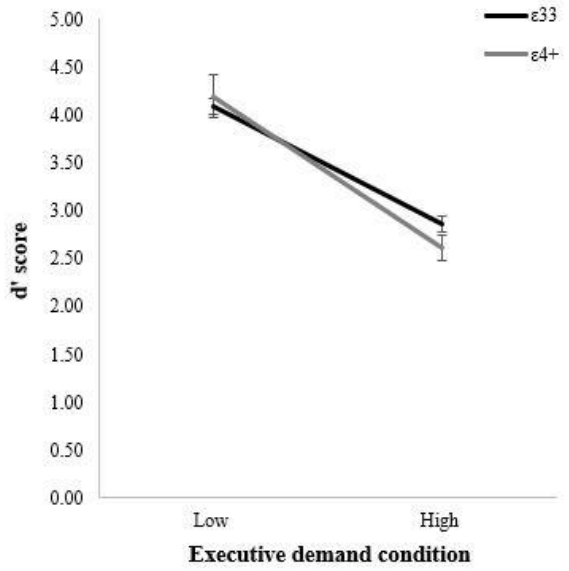

Fig. 5. *d'* scores between executive demand conditions, by *APOE* genotype (+/- 1SEM)

3.3.5. Subjective task difficulty

Across all participants, effort ratings in the HE condition (mean rating 77.18) were significantly higher than effort ratings in LE condition (mean rating 61.37), $t(110) = -10.61$, $p < .001$, $d = 1.02$.

There were no genotype differences in effort ratings in the LE condition, $t(82) = 0.85$, $p = .40$, $d = 0.21$, or HE condition, $t(82) = 0.70$, $p = .49$, $d = 0.18$.

3.4. Prospective memory task

3.4.1. Baseline decision-making

3.4.1.1. Accuracy. Across the whole sample, decision-making accuracy did not change between the low executive demand (LE: no decision switching) and high executive demand (HE: decision switching) conditions, $t(107) = 0.59$, $p = .56$, $d = 0.06$.

There were no genotype differences in decision-making accuracy, $F(1,79) = 0.44$, $p = .51$, $\eta^2_p = .01$, nor any genotype*demand condition interaction on decision-making accuracy, $F(1,79) = 0.07$, $p = .79$, $\eta^2_p = .001$.

3.4.1.2. Reaction times. Across the whole sample, reaction time to correct decisions was faster in the LE (mean 928.69 ms) compared to the HE condition (mean 1128.02 ms), $t(107) = -11.15$, $p < .001$, $d = 1.11$.

No genotype differences in reaction times to correct decisions were seen, $F(1,82) = 1.89$, $p = .17$, $\eta^2_p = .02$, nor any genotype*demand interaction on reaction times to correct decisions, $F(1,82) = 0.02$, $p = .89$, $\eta^2_p = .00$.

3.4.2. Prospective memory performance

Holding a PM intention resulted in a significant decrease in accuracy and increase in reaction times when responding to the ongoing decision-making trials, in both the LE and HE conditions (all $p < .001$). As there was a significant decrease in performance between the ongoing block and the PM block, a PM cost score was calculated for both accuracy and RT. Prospective memory results are shown in Table 4, by APOE genotype.

Table 4
Prospective memory performance, by APOE genotype

APOE	Executive demand	Accuracy performance (% correct)			Reaction time performance (ms)		
		DM	DM + PM	PM cost	DM	DM + PM	PM cost
ε33	Low (no switching)	94.31	91.72	2.60	917.00	1087.93	170.93
		(3.30)	(4.55)	(3.25)	(132.97)	(233.06)	(152.17)
	High (switching)	94.3	91.26	3.04	1126.10	1398.99	272.88
		(3.66)	(4.54)	(3.44)	(220.32)	(283.50)	(205.86)
ε4+	Low (no switching)	92.4	90.91	1.49	982.65	1131.12	148.47
		(6.08)	(4.55)	(5.04)	(230.18)	(229.43)	(118.62)
	High (switching)	92.72	88.57	4.16	1184.82	1352.53	167.71
		(6.88)	(6.58)	(3.01)	(292.19)	(378.85)	(225.83)

Note: Mean (SD). Decision-making (DM). Prospective memory (PM)

3.4.2.1. Prospective memory hits. PM accuracy was higher in the low demand (*Mdn* = 2) than the high demand (*Mdn* = 1) condition, $z = 1217.50$, $p = .03$.

PM hits did not differ between ε33 (*Mdn* = 2) and ε4+ carriers (*Mdn* =1) in the LE condition, $U = 542.50$, $z = -1.28$, $p = .20$. In the HE condition, there was also no difference in PM hits between ε33 (*Mdn* = 1) and ε4+ carriers (*Mdn* =1), $U = 556.50$, $z = -1.13$, $p = .26$.

3.4.3. Cost of PM intention on baseline decision-making

3.4.3.1. Accuracy cost. Cost was calculated as a dichotomous variable (cost/no cost shown). There were no genotype differences in the percentage of ε4+ carriers (66.7%) compared to ε33 carriers (77.8%) showing a cost of holding a PM intention on decision-making accuracy in the LE condition ($p = .38$, Fisher's Exact Test), nor in the percentage of ε4+ carriers (90.5%) compared to ε33 carriers (84.1%) showing a cost of holding a PM intention on decision-making accuracy in the HE condition ($p = .72$, Fisher's Exact Test).

3.4.3.2. Reaction times cost. Cost was calculated as a dichotomous variable (cost/no cost shown). There was a significant between genotype difference on RT in the HE condition only: a larger percentage of ε4+ carriers (33.3%) compared to ε33 carriers (9.5%) showed no cost of holding a PM intention on decision-making reaction times ($p = .02$, Fisher's Exact Test). Based on the odds ratio, for ε33 carriers the odds of showing a cost was 4.75 times more likely than for ε4 carriers. There was no difference in the LE condition ($p = .28$, Fisher's Exact Test).

3.4.3.3. Switching errors cost (high executive demand condition only). Holding a PM intention was associated with increased switching errors, with ε4 carriers showing a greater increase (M = 5.26) in switching errors than ε33 carriers (M = 2.08), $t(81) = -2.21$, $p = .04$, $d = 0.62$.

3.4.4. Subjective task difficulty

Across all participants, effort ratings in the HE condition (mean rating 68.14) were significantly higher than effort ratings in LE condition (mean rating 56.10), $F(1,107) = 79.90$, $p<.001$, $\eta^2_p = .43$, and effort ratings in the prospective memory block (mean rating 66.81) were significantly higher than effort ratings in the ongoing block (mean rating 57.44), $F(1,107) = 69.94$, $p<.001$, $\eta^2_p = .40$. There was a demand condition*block interaction, $F(1,107) = 10.65$, $p = .001$, $\eta^2_p = .09$, such that there was a lower difference in effort ratings between the ongoing and prospective memory blocks in the HE condition. There were no genotype differences in effort ratings across task blocks or demand conditions (all $p > .05$).

4. Discussion

This study aimed to examine whether responses to systematically manipulated executive function (EF) demands differ by *APOE* genotype in young adulthood. The novelty of the present study is the manipulation of EF requirements embedded within decision-making, sustained attention, verbal fluency, and prospective memory tasks, allowing the examination of the interaction of EF processes and *APOE* genotype within complex cognitive paradigms.

The current study found that in young adults, carrying an ε4+ allele is associated with differences in EF; however, these differences varied depending on the cognitive process targeted and the level of task demand. Two main findings emerged; first, that ε4+ carriers demonstrated better working memory updating abilities when task demands were lower; second, that ε4+ exhibited more effective resource allocation and greater strategy use then ε33 when task demands were higher.

Specifically, despite no genotype differences in correct word production in the verbal fluency task, working memory (WM) updating advantages were indicated in young ε4+ carriers through lower rates of repeated words [65]. In the high executive demand condition, however, more ε4+ than ε33 carriers produced root repetition errors. Whilst this may suggest

that ε4+ carriers were generally more prone to performance errors under higher levels of demand, this error type is indicative of less precise rule application being used to facilitate greater phonemic clustering as a word production stratagem. Therefore, an alternative and preferred explanation for this genotype difference is that more ε4+ carriers than ε33 carriers applied phonemic clustering and less rigorous lexical filtering as a cognitive strategy [66]. Notably, in ε4+ carriers we saw updating advantages under conditions of low executive demand whilst strategy use emerged under conditions of high executive demand; ε4+ carriers appear to be using EF advantages to outperform ε33 carriers when task demands are lower, then applying phonemic strategies to *maintain* performance when task demands are higher. Furthermore, whilst no other young ε4+ research has looked at error types within the verbal fluency task, observations of young ε4+ advantages in sustained attention and spatial memory tasks consistent with working memory updating have been reported [5,9,11,12].

It is surprising that we did not replicate earlier findings of ε4+ advantages in overall correct words produced, as this is a relatively consistent finding in young adults [3,5,8,11,29], although there are exceptions [12,13]. The metrics used in scoring verbal fluency, regarding classification of correct words vs errors, are somewhat subjective, which may explain these inconsistent results. Accordingly, our scoring scheme was stricter and was validated through a consensus of three raters.

A sustained attention paradigm previously reporting young ε4+ advantages [5,9] was modified for use in the current study. Contrasting with the previous outcomes we observed no ε4+ advantage in correct hits or target detection. In line with Rusted et al. [9], ε4+ produced fewer false alarms than ε33 in the low demand condition, and a greater increase in false alarms from the low engagement to the high engagement condition, suggestive of a speed-accuracy trade-off. Furthermore, both genotype groups showed a decline in target detection (after accounting for response bias) from conditions of low to high executive demand, although robust analyses suggest this result should be interpreted with caution. Notably, an imaging study using the same sustained attention paradigm as the current study also reported no genotype behavioural differences in correct hits or target detection in young adults but instead saw different patterns of activation and cognitive effort indexed through pupillometry, suggestive of different cognitive strategies across genotypes [67].

Our results also showed that ε4+ were less disadvantaged than ε33 when performing the concurrent decision-making and prospective memory tasks; fewer ε4+ showed a cost to reaction times due to performing both tasks simultaneously, indicating that ε4+ show more effective allocation of cognitive control resources [68]. This is the first study to report

reduced dual task cost in young ε4+ PM performance, and contrasts the finding that by middle-age, ε4+ show a greater cost of holding a PM intention than ε33 [69].

Importantly, under the highest level of executive demand (i.e. when concurrently performing decision-making, prospective memory, and switching tasks) we saw ε4+ making more errors than their ε33 peers. Yet, the combination of higher ε4+ switching errors in the absence of genotype differences in decision-making accuracy or reaction time is indicative of a speed-accuracy trade-off, an executive strategy that may again suggest differences in resource allocation, with ε4+ working harder to maintain the same performance as ε33 carriers. This interpretation is strengthened by the finding that ε4+ also showed a greater increase in false alarms as task demand increased in the sustained attention task.

Both the reduced cost of performing concurrent tasks and the application of a speed-accuracy trade-off as a cognitive strategy are consistent with ε4+ differences in allocation of cognitive resources. Interestingly, Evans et al. [70] saw a greater slowing of ε4+ reaction times from young to middle-aged adulthood (in a cross-sectional analysis), despite ε4+ showing greater accuracy than ε33 carriers in middle age. We suggest that complex tasks combining heightened executive demand across multiple cognitive processes may be inducing an ε4+ response more akin to middle-aged functioning in our young adult ε4+ carriers.

Importantly, ε4+ strategy differences (whether phonemic clustering or speed-accuracy trade-offs) were only evident under conditions of high executive demand, where such strategies would be of most benefit. In the decision-making task, only the high executive demand condition involved trial-by-trial switching, therefore switching errors could only occur in the high executive demand condition. However, it was only with the addition of the prospective memory component that ε4+ produced a greater number of switching errors than ε33. Again, only with increased pressure on resource allocation (enforced by concurrent decision-making, prospective memory, and motor switching tasks) did ε4+ change strategies, and in doing so maintained their overall performance at the same level as ε33. Within the sustained attention task, the same pattern was seen with high demand inducing a speed-accuracy trade-off; strategy modification occurred from low to high task demand, reflected in a greater ε4+ decrease in performance. Previously, Nao et al. [71] interrogated three central features of EF; they reported no genotype differences in updating and monitoring of working memory, response inhibition, and saw an ε33 advantage in task switching. In contrast, Sinclair et al. [43] investigated different levels of demand in young adult ε4+, finding genotype differences on an n-back working memory task requiring updating, suggestive of a

possible young ε4+ speed-accuracy trade-off, although no obvious pattern was highlighted through different levels of n-back demand. In the current study, the use of complex paradigms exposed EF advantages under conditions of lower EF demand, and strategic and resource allocation differences under conditions of elevated EF demand.

Given the appearance of heightened ε4+ cognitive control and strategy use only under conditions of elevated executive demand, it may be that the ε4+ use of cognitive strategies is a form of compensatory processing. Whilst previous research argues against ε4+ consciously compensating for cognitive deficits [5], compensatory mechanisms have frequently been suggested as an interpretation of patterns of activation in imaging studies [6,25,72–74]. To speculate, compensatory mechanisms may reflect greater ε4+ DMN downregulation (e.g. [75]). Whilst our behavioural results do not directly address the mechanisms underlying genotype differences in performance nor how young ε4+ neural compensation relates to later ageing processes, our findings highlight the importance of identifying whether strategy differences in young adult ε4+ carriers drive or reflect accelerated ageing.

Limitations of this study include the small sample size of our ε4+ group, which precluded dose-response analyses by *APOE* allele. Yet, studies showing APOE cognitive differences have spanned both large and smaller sample sizes; whilst studies using the largest samples (containing between 343 and 1345 ε4+ carriers) failed to see any genotype differences [17, 19, 21], these studies all used general cognitive batteries. Considering only studies using more sensitive cognitive measures, a large study of 542 ε34 carriers saw an ε34 advantage [43], and ε4+ advantages have been seen in moderately sized samples of 50 ε4+ carriers [3], and samples containing between 21 and 42 ε4+ carriers [4, 5, 8, 9, 11, 12].

Our results highlight important differences in executive responses to task difficulty across *APOE* genotypes, using a novel executive demand paradigm. The paradigm was shown to work as anticipated in the larger study sample, and therefore, since ε4+/ε33 groups did not differ from the ε4+ group in any demographic characteristics except sex, we believe we can confidently attribute performance differences observed within the genotype subgroup to *APOE* genotype. Nevertheless, replication of our sensitive executive demand paradigm in a larger sample would be of value.

The sample size in the present study precluded opportunities to analyse the data by sex, and so we are unable to make any inferences about potential genotype and sex interactions. It may be that sex-specific APOE effects underlie the genotype differences observed (such that ε4 females were demonstrating differential cognitive responses compared with ε33 males and females, and ε4 males). Yet, there is no consistent pattern of

genotype*sex interactions in youth; findings span female ε4+ structural covariance differences [12], elevated male ε4+ cognitive performance [28], no sex differences in cognitive performance [11,14,20], as well as genotype differences identified when using both all or mainly male samples [10,24] and matched samples [3,5,6].

Finally, especially given emerging evidence of genotype differences in early-life gain from protective factors including education [76,77] and known differences in APOE genotype allelic frequencies and risk of poorer cognitive ageing by ethnicity [78], by design our participant group was constrained to highly educated Caucasian individuals in order to minimise potential confounds. This reduces the representativeness of our sample to the wider population, and future research in larger samples would benefit from also including less educated individuals and all ethnicities.

4.1. Conclusions

Taken together, these results suggest that in young adults, ε4+ carriers show better working memory updating at lower levels of executive demand. As levels of executive demand increase, ε4+ seem to allocate resources more efficiently and employ strategies, such as a speed-accuracy trade-off, to maintain performance equivalent to their ε33 counterparts.

These findings support the notion that the impact of ε4+ on cognitive function in young adults is process specific, whilst broad suggestions of ε4+ cognitive advantages in youth (e.g. antagonistic pleiotropy [79]) are likely too simplistic. That we can identify distinct ε4+ effects in young adults aids understanding of the impact of APOE ε4 on cognitive function across the lifespan. Further insight would be gained by investigating whether differential APOE responses to executive demand persist into mid-adulthood and whether APOE responses to executive demand may act as an early marker for later cognitive decline.

More work is needed to identify the neurocognitive mechanisms underpinning the differences reported here. Previous literature suggests speed-accuracy trade-offs may reflect a compensatory process; therefore, use of these sensitive and complex executive demand tasks in an fMRI paradigm would be of value to determine whether such compensatory mechanisms are employed in response to different levels of executive demand. Furthermore, the present results raise questions about the later-life impact of engaging compensatory processes earlier in the lifespan, and whether this contributes to the ε4+ susceptibility to poor cognitive ageing. Future research needs to establish the nature and aetiology of increased risk

of poorer ε4+ cognitive ageing, as well as to identify potential neural targets for tailored early-life interventions to reduce ε4+ risk of later life cognitive decline.

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Appendix: Modified Cognitive Reserve Index

Please think back to primary school age (between 4-11 years old)

Please think back to secondary school age (between 12-17 years old)

HOW OFTEN at that age did you perform each of the activities listed below?

Please choose an option for either weekly, monthly, or yearly frequency.

	3 times a week or more	2 times a week or less	3 times a month or more	2 times a month or less	3 times a year or more	2 times a year or less
Reading newspapers/magazines/comics						
Housework activities (cooking, cleaning, washing, ironing etc.)						
Reading books						
Leisure activities - physical (sports, dancing, bowling etc.)						
Leisure activities - other (board games, cards etc.)						
Using technologies (computer, games console, mobile phone etc.)						
Social activities (parties, going out with friends, local community events etc.)						
Cinema, theatre						
Crafts and gardening (handicraft, knitting, embroidery etc.)						
Taking care of children or elderly						
Volunteering						
Artistic activities (playing an instrument, singing, painting, writing, etc.)						
Exhibitions, concerts, conferences						
Holidays (lasting at least several days)						